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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,328	02/12/2002	Jeff Steven Grotelueschen Hall	FORS-06930	5712

23535 7590 11/08/2005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,328	GROTELUESCHEN HALL ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-106 and 111-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-106 and 111-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/8/2005 has been entered.

2. Currently, claims 101-106 and 111-125 are pending in the instant office action. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not maintained have been rendered moot by the amendments to the claims filed 7/28/2005. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. Claims 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The preliminary amendment filed 2/12/2002 canceled claims filed with the original application and added new claims without designating where such amendments are supported by the specification. Instant claims 102 and 103 recite where the 3' portion of said second oligonucleotide comprises or consists of a 3' terminal nucleotide not complementary to said target, however support for such amendment could not be found in the specification or the claims as originally filed. Figure 32 provides an embodiment of the invention wherein the 3' portion of the 2nd oligonucleotide is not hybridized to the target, however it's 3' terminus, and 3' portion as well, are complementary to the target. At page 14, the specification teaches that the first or second oligonucleotides are partially complementary to the RNA, however the specification does not teach that the 3' terminal nucleotide is not complementary. Therefore, the addition of claims 102 and 103 appear to add new matter to the claimed invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 101-106 and 111-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 101 has been amended to recite "5' nuclease", however the term is vague and indefinite as it is unclear what type of nucleases such refers to. The specification does not provide a definition of such term, but instead teaches at page 40, that "the structure dependent

single stranded endonuclease activity of a DNA polymerase is more properly referred to as a 5' nuclease", and also that "...the nuclease activity associated with some thermostable DNA polymerases cleaves endonucleolytically but this cleavage requires contact with the 5' end of the molecule being cleaved. Therefore, these nucleases are referred to as 5' nucleases." Such teaching only provides examples of possible 5' nucleases but does not define the scope of a 5' nuclease. It is unclear from the examples in the specification, if such term encompasses exonucleases, or only endonucleases that require a 5' end. Is exonuclease 1, a 5'-3 exonuclease considered a 5' nuclease? Is any 5'-3' exonuclease (which inherently requires a 5' end) considered a 5' nuclease? The metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

7. Claims 101-104, 111-117, and 123-125 rejected under 35 U.S.C. 102(b) as being anticipated by Harrington (Harrington et al.; The EMBO Journal, vol 13, pp 1235-1246, 1994).

With regard to claim 101, Harrington teaches a set of oligonucleotides as follows: 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5) (claims 114-115, it is noted that the claims do not require that the first and second target be different, therefore more than one copy of the target nucleic acid can be considered first, second, third, etc, target nucleic acids. Alternatively, any of the other nucleic acids taught by Harrington - see page1245, col 1"oligonucleotides"- can be considered a second "target" nucleic acid, as claim 115 does not provide any structural limitations with regard to the "second target nucleic acid"), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group;

with regard to claim 125, HJ40 comprises an uncleavable region) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. With regard to claims 102 and 103, Harrington teaches a second oligonucleotide which comprises and consists of a single nucleotide not complementary to the target. With regard to claim 104, Harrington teaches administering such oligonucleotides to a gel, which is considered a solid support. With regard to claim 112, Harrington teaches a buffer solution (see page 1245). With regard to claim 113, Harrington teaches a third oligonucleotide HJ49, complementary to a third region of said target nucleic acid upstream of said first region of said target nucleic acid. It is noted that the term "providing" in claim 113 has been given no weight as the claims are drawn to products and not to methods requiring a step such as "providing". With regard to claim 116, the claim sets forth no structural limitations for "linker". Therefore the term has been given it's broadest reasonable meaning which encompasses the sugar group of the nucleotide. With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, molecule HJ42 comprises a label at it's 5' end (claim 123). With regard to claim 124, either HJ42 or HJ40 comprise an uncleavable region.

8. Claims 101-104, 111-117, and 123-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrington II (Harrington et al; Journal of Biological Chemistry, vol. 270, pp 4503-4508, 1995).

With regard to claim 101, Harrington II teaches a set of oligonucleotides as follows: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15) (claims 114-115, it is noted that the claims do not require that the first and second target be different, therefore more than one copy of the target nucleic acid can be considered first, second, third, etc, target nucleic acids. Alternatively, any of the other nucleic acids taught by Harrington - see page4503, col 2 "oligonucleotides"- can be considered a second "target" nucleic acid, as claim 115 does not provide any structural limitations with regard to the "second target nucleic acid"), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group; with regard to claim 125, HJ46 comprises an uncleavable region); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. With regard to claims 102 and 103, Harrington II teaches a second oligonucleotide, HJ77, which comprises and consists of a single nucleotide not complementary

to the target. With regard to claim 104, Harrington II teaches administering such oligonucleotides to a gel, which is considered a solid support. With regard to claim 112, Harrington II teaches a buffer solution (see page 4504). With regard to claim 116, the claim sets forth no structural limitations for "linker". Therefore the term has been given it's broadest reasonable meaning which encompasses the sugar group of the nucleotide. With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, molecule HJ46 comprises a label at it's 5' end (claim 123). With regard to claim 124, HJ46 comprises an uncleavable region as it comprises regions not cleaved in the reaction.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington in view of Dahlberg (WO 94/29482).

Harrington teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington teaches among other reagents: 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington does not teach a method wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support, however Dahlberg teaches a method wherein cleavage structures as taught by Harrington are subjected to cleavage reactions with 5' nucleases, as taught by Harrington wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleaves structures

are released from the immobilized structure for further analysis. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to immobilize the first or second oligonucleotide taught by Harrington to a solid support as taught by Dahlberg. The ordinary artisan would have been motivated to attach either the first or second oligonucleotide in the cleavage structures of Harrington to a solid support as taught by Dahlberg for ease of cleavage detection as taught by Dahlberg.

12. Claims 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Dahlberg.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both; and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to

be limited to stability at any particular temperature. Harrington II does not teach assays wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support, however Dahlberg teaches a method wherein cleavage structures as taught by Harrington are subjected to cleavage reactions with 5' nucleases, as taught by Harrington II wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to immobilize the first or second oligonucleotide taught by Harrington II to a solid support as taught by Dahlberg. The ordinary artisan would have been motivated to attach either the first or second oligonucleotide in the cleavage structures of Harrington II to a solid support as taught by Dahlberg for ease of cleavage detection as taught by Dahlberg.

13. Claims 105-106, 118-119 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington in view of Urdea.

Harrington teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington teaches among other reagents, 1) a target nucleic acid HJ41 (Figure 8a, lanes 3-5), 2) a first oligonucleotide HJ40 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group) alternatively, HJ42 can be considered a first oligonucleotide as it comprises a portion completely

complementary a first region of a target nucleic acid; 3) a second oligonucleotide HJ39, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism (claim 111). It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington does not teach a method wherein the first oligonucleotide (claim 105) or the second oligonucleotide (claim 106) is attached to a solid support or wherein the first oligonucleotide comprising a charged adduct comprises a detectable molecule which is flourescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and 3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Harrington with fluorescein on an amino modified base, and to attach either the first oligonucleotide or the second oligonucleotide on a solid support as taught by Urdea because Urdea teaches detection of cleaved nucleic acids by separation of a labeled nucleic acid from a solid support and teaches labels such as fluorescein on an amino modified base can be

used. The ordinary artisan would have been motivated to improve the method of Harrington with the use of the solid support and labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactively labels.

14. Claims 105-106, 118-119, and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Urdea.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both, and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington II does not teach a method wherein the first oligonucleotide (claims 105) or the second oligonucleotide (claim 106) is attached to a solid support or wherein the first oligonucleotide comprising a charged adduct

comprises a detectable molecule which is flourescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and 3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Harrington II with fluorescein on an amino modified base, and to attach either the first oligonucleotide or the second oligonucleotide on a solid support as taught by Urdea because Urdea teaches detection of cleaved nucleic acids by separation of a labeled nucleic acid from a solid support and teaches labels such as fluorescein on an amino modified base can be used. The ordinary artisan would have been motivated to improve the method of Harrington II with the use of the solid support and labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactive labels.

15. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington in view of Corey.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini or 5' termini and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to

the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington does not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased Ka by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the assays of Harrington with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Harrington, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Harrington for the purpose of accelerating hybridization, as taught by Corey, in the assays of Harrington, and thus enhancing the assays of Harrington.

16. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington II in view of Corey.

Harrington II teaches a set of oligonucleotide structures that include nucleic acid sequences with unhybridized 3' termini, 5' termini, or both, and teaches analysis of cleavage of such structures using a 5' nuclease lacking synthetic activity. Harrington II teaches among other reagents: 1) a target nucleic acid AI4 (Figure 5a, lanes 11-14; 5b, lanes 11-15), 2) a first oligonucleotide HJ46 comprising a charged adduct and a portion completely complementary to the target (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group); 3) a second oligonucleotide HJ77, comprising a 3' portion and a 5' portion completely complementary to a second region of the target nucleic acid downstream of and contiguous to said first region; and 4) FEN-1, a thermostable 5' nuclease lacking synthetic activity which comprises an amino acid sequence wherein a portion is homologous to a portion of an amino acid sequence of a thermostable DNA polymerase derived from a thermophilic organism. It is noted that the term thermostable has been broadly interpreted to encompass a nuclease which is stable at a specific temperature. The specification does not define the term to be limited to stability at any particular temperature. Harrington II does not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased Ka by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the

assays of Harrington II with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Harrington II, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Harrington II for the purpose of accelerating hybridization, as taught by Corey, in the assays of Harrington II, and thus enhancing the assays of Harrington II.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 101-106 and 111-125 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 13-18, and 21-23 of U.S. Patent No. 6,872,816. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target

downstream of and contiguous to the first region of the target. Claims 1 and 9 of the '816 patent are drawn to a kit (a set of reagents) comprising a thermostable Flap endonuclease (a thermostable 5' nuclease lacking synthetic activity); a first oligonucleotide which comprises a 3' portion completely complementary to a first region of the target (which inherently comprises a charged adduct, any charged group such as a single nucleotide or charged phosphate group); and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target, downstream of and contiguous to the first region of the target. It is noted that claims 102-106 and 111-115 of the instant application are identical to claims 6-7, 13, and 15-18 of the '816 patent. Additionally, as defined by the specification of the '816 patent, the oligonucleotides encompass a charged adduct, including a linker, a detectable molecule, an amino acid, an amino modified base and an uncleavable region. Accordingly, the claims of the '816 patent and the claims of the instant application are coextensive in scope and the claims of the '816 patent represent a species of the genus claimed in the instant application. The courts have stated that a genus is obvious in view of the teaching of a species. See Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

19. Claims 101-106 and 111-125 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33-39 and 42-43 of U.S. Patent No. 6,562,611. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking

synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claim 33 of the '611 patent kit drawn to a kit (a set of reagents) comprising Fen 1 endonuclease (a thermostable 5' nuclease lacking synthetic activity); a first oligonucleotide which comprises a 5' portion complementary to a first portion of the target (which inherently comprises a charged adduct, any charged group such as a single nucleotide or charged phosphate group); and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is complementary to a second portion of the target, downstream of and contiguous to the first portion of the target. It is noted that claims 102-106 and 112-113 of the instant application are identical to claims 34-39 and 42 of the '611 patent and claims 111 and 114-115 of the instant application encompass the teaching of claims 33 and 43 of the '611 patent. Additionally, as defined by the specification of the '611 patent, the oligonucleotides encompass a charged adduct, including a linker, a detectable molecule, an amino acid, an amino modified base and an uncleavable region. Accordingly, the claims of the '611 patent and the claims of the instant application are coextensive in scope and the claims of the '611 patent represent a species of the genus claimed in the instant application. The courts have stated that a genus is obvious in view of the teaching of a species. See Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

20. Claims 101-103 and 111-125 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 of U.S. Patent No. 6,913,881. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 6-9 of the '881 patent are drawn to a kit (a set of reagents) comprising a cleavage agent, and first and second oligonucleotides wherein the first oligonucleotide which comprises a 5' portion complementary to a first region of the target (which inherently comprises a charged adduct, any charged group such as a single nucleotide or charged phosphate group); and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is complementary to a second region of the target, downstream of and contiguous to the first region of the target. As defined by the specification of the '881 patent, the cleavage agent encompass a thermostable 5' nuclease lacking synthetic activity (eg: FEN-1); and the oligonucleotides encompass a charged adduct, including a linker, a detectable molecule, an amino acid, an amino modified base and an uncleavable region; and the second oligonucleotide comprises or consists of a 3' terminal nucleotide not complementary to the target. Accordingly, the claims of the '816 patent and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

21. Claims 104-106 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 of U.S. Patent No. 6,913,881 in view of Dahlberg. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 6-9 of the '881 patent are drawn to a kit (a set of reagents) comprising a cleavage agent, and first and second oligonucleotides wherein the first oligonucleotide which comprises a 5' portion complementary to a first region of the target (which inherently comprises a charged adduct, any charged group such as a single nucleotide or charged phosphate group); and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is complementary to a second region of the target, downstream of and contiguous to the first region of the target. As defined by the specification of the '881 patent, the cleavage agent encompass a thermostable 5' nuclease lacking synthetic activity (eg: FEN-1). Although the claims of the '881 patent do not teach oligonucleotides attached to a solid support, Dahlberg teaches a method wherein cleavage structures as taught by the '881 patent are subjected to cleavage reactions with 5' nucleases, wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

immobilize the first or second oligonucleotide taught by the claims of the '881 patent to a solid support as taught by Dahlberg. The ordinary artisan would have been motivated to attach either the first or second oligonucleotide in the cleavage structures of the claims of the '881 patent to a solid support as taught by Dahlberg for ease of cleavage detection as taught by Dahlberg.

22. Claims 101-106 and 111-125 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 35-36, 44-46, and 49-50 of copending Application No. 11/103,943. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 26, 35 and 36 of the '943 application are drawn to a composition (a set of reagents) comprising a thermostable Flap endonuclease (a thermostable 5' nuclease lacking synthetic activity); a nucleic acid molecule which hybridizes to the first region of the target, upstream of an oligonucleotide probe (which inherently comprises a portion complementary to a first region of the target and inherently comprises a charged adduct, any charged group such as a single nucleotide or charged phosphate group); and an oligonucleotide probe comprising a 3' portion and a 5' portion wherein the 5' portion is configured to hybridize to a second region of the target, downstream of and contiguous to the first region of the target (which inherently comprises a 5'

portion complementary to a second region of the target). It is noted that claims 104-106, 114 and 117 of the instant application are coextensive in scope with claims 45-46 and 49-50 of the '943 application. Additionally, as defined by the specification of the '943 application, the oligonucleotides encompass a charged adduct, including a linker, a detectable molecule, an amino acid, an amino modified base and an uncleavable region. Accordingly, the claims of the '943 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims 101-106, 111-120 and 122-125 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/031,487. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which comprises a 5' portion and a 3'

portion wherein the 5' portion hybridizes to the HCV 5' UTR and it's 3' portion does not. As defined by the specification of the '487 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '487 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/031,487 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second

oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and it's 3' portion does not. As defined by the specification of the '487 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '487 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '487 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '487 application.

This is a provisional obviousness-type double patenting rejection.

25. Claims 101-106, 111-120, and 122-125 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide

comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '408 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target

nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '408 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '408 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '408 application

This is a provisional obviousness-type double patenting rejection.

Conclusion

27. No claims are allowable over the cited prior art.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

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10/29/05